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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/475,704	12/30/1999	SUSAN W. BARNETT	1631.002	6738

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Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/475,704	BARNETT ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,24-43,49-60 and 63-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,24-43,49-60,63-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/20/04 has been entered.

Claims 1-10, 24-43, 49-60, and 63-75 are pending.

Applicants' traversal, the amendment to claims 1, 2, 3, 4, 6-9, 24, 27, 41, 59, and 63, the cancellation of claim 62 in paper filed on 5/20/04 is acknowledged and considered.

The indicated allowability of claims 68-73 is withdrawn in view of the newly discovered reference(s) to pre-grant US publication 2003/0138453 (which Dr. Barnett is listed as a co-inventor and the publication was not cited on a PTO-1449). Rejections based on the newly cited reference(s) follow.

Specification

The disclosure remains objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The amendment filed on

8/23/03 to page 18 is acknowledged. However, the specification still contains an embedded hyperlink on pages 26 and 69.

Claim Objections

Claim 24 is objected to because of the following informalities: there are two commas after the term "claim 3". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-10, 24-43, 49-60, and 63-66 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 7-10, 24-43, 49-60, and 63-66, as best understood, are readable on a genus of a polynucleotide sequence encoding a HIV Gag polypeptide that elicits a Gag-specific immune response, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3, or 4, wherein the genus of polynucleotide sequences is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Gag polypeptide, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3, or 4. The as-filed specification provides sufficient description of an immunogenic HIV Gag polypeptide set forth in SEQ ID NO: 3 or 4 and fragments of SEQ ID NO: 3 (SEQ ID NO: 1) and fragment of SEQ ID NO: 4 (SEQ ID NO: 2). The specification does not define the term "an HIV Gag polypeptide that elicits a Gag-specific immune response". The specification defines an "immunological response" as humoral and/or cellular immune response (page 14) and the cellular immune response could include a response with CD4+ cells and/or CD8+ cells. The specification does not disclose which nucleotides are considered essential for eliciting a humoral and/or cellular immune response. For example, the specification does not disclose what peptides encoded by SEQ ID NOs: 1-4 elicit a humoral and/or cellular immune response. Furthermore, the as-filed specification and the art of record teach that Gag proteins of HIV are necessary for the assembly of virus-like particles and HIV Gag proteins are involved in many stages of the life cycle of the virus including assembly, virion manufacture after particle release, and early post-entry step in virus replication. The role of HIV Gag proteins are numerous and complex (IDS, Freed, Virology, 1998). The specification contemplates that synthetic HIV Gag polypeptides can be measured for virus-like particle (VLP) production (page 29). In addition, in view of the

phrase "HIV Gag polypeptide", the polypeptide has to be identical (same function) to one found in an HIV in nature. The specification does not disclose how to distinguish between a sequence with natural HIV Gag polypeptide activity and an HIV Gag polypeptide that does not have Gag activity that is also at least 90% identical to the claimed sequences. One skilled can envision a sequence that is at least 90% identical to the claimed SEQ ID NOs., but would be unable to determine if the sequence had a function that was considered part of the claimed genus of DNA molecules. In addition, on the amino acid level, there is even a larger variation than 90% identity to the polynucleotide sequences (70% with respect to substitutions and not including deletions and insertions), indicating a variation in the claimed genus of polynucleotide sequences. Determining 70% identity at the amino acid level from 90% at the polynucleotide level was based on the following: substituting 100 nucleotides of a 1,000 base pair polynucleotide sequence is a sequence with 90% identity to the 1,000 base pair polynucleotide sequence. The polypeptide sequence encoded by the polynucleotide sequence with 90% identity would have a polypeptide with 333 amino acids. Substitute one polynucleotide in 100 codons of the polynucleotide with 90% identity would be a polypeptide with 30% substitution. Thus, in view of the reasons set forth above and the numerous and complex functions of HIV Gag polypeptides, the variation within the claimed genus of polynucleotide sequences, the specification does not disclose which activities of HIV gag correspond to the claimed genus of polynucleotides with 90% sequence identity to the claimed SEQ ID NOs.

It is apparent that on the basis of applicants' disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are

essential for the genus of polynucleotide sequences as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of polynucleotide sequences that must exhibit the disclosed biological functions as contemplated by the claims.

The mere contemplation of the claimed genus in the specification is not sufficient to support the present claimed invention directed to a genus of a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Gag polypeptide, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3, or 4. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of polynucleotide sequences that must possess the biological properties as contemplated by applicants' disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a polynucleotide sequence encoding an HIV Gag polypeptide that elicits a Gag-specific immune response, wherein the polynucleotide

sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3, or 4 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 5/20/04 have been fully considered but they are not persuasive.

Applicants argue that the specification clearly describes the structure and function of the claimed biomolecules polynucleotides and that the correlation between structure and function is also disclosed (immunogenic regions of Gag were known and could readily be determined. See Ulmer Declaration, paragraph 18 and Exhibit E and F). The argument is not found persuasive because neither the teaching of Parker nor the teaching of Johnson are described in the specification. Parker teaches a scheme for ranking potential HLA-A2 binding peptide based on independent binding of individual side-chains using synthetic nonamer peptides. Parker does not teach that immunogenic regions of Gag were known at the time the invention was made. The specification does not describe using the scheme taught by Parker for determining which amino acids of an HIV Gag polypeptide comprising a polypeptide encoded by SEQ ID NOs: 1-4 are required for eliciting a Gag-specific immune response. Johnson identifies epitopes in the HIV-1 gag protein and the heterogeneity of CTL responses to this protein. Johnson further teaches that, "Although it appears likely that CTL specific for these conserved gag epitopes will recognize

sequences from a variety of HIV-1 isolates, prior studies of the consequences of aa variation in HIV-1 epitopes have shown variable effects on recognition by human HIV-1 specific CTL (page 1519)." The specification does not disclose how to correlate the epitopes from the HIV-gag proteins taught by Johnson with the claimed polynucleotide sequences. See MPEP 608.01(p). Neither Parker nor Johnson describe which nucleotides or amino acids are considered essential for an HIV Gag polypeptide to elicit a cellular and/or a humoral immune response.

Applicants argue that the function of the polypeptide encoded by the claimed genus of polynucleotides is now more clearly set forth as immunogenic function rather than all biological functions. The argument is not found persuasive because the specification does not define the limitation "a Gag-specific immune response". The specification does not disclose which nucleotides of the claimed sequences are considered essential for eliciting a humoral and/or cellular immune response. Furthermore, the argument is not found persuasive because the claims still read on a genus of polynucleotides that encode an HIV Gag polypeptide that elicits a specific Gag immune response and has the biological function(s) of a natural Gag polypeptide. As stated above, the as-filed specification and the prior art teach that Gag proteins of HIV are necessary for the assembly of virus-like particles and HIV Gag proteins are involved in many stages of the life cycle of the virus including assembly, virion manufacture after particle release, and early post-entry step in virus replication. The role of HIV Gag proteins are numerous and complex (IDS, Freed, Virology, 1998). In addition, the specification does not describe which amino acids of the claimed HIV gag polypeptide encoding sequences are required for its biological activity and are required for an HIV Gag polypeptide to elicit a Gag-specific immune response.

With respect to applicants' argument that in view of Example 14 in the Patent Office's "Synopsis of Application of Written Description Guidelines" the specification has written support. The argument is not found persuasive because the specification does not provide sufficient description of the claimed genus of polynucleotides. The pages cited for support of the claimed genus of sequences do not provide assays for determining whether a polypeptide elicits a Gag specific immune response. The specification does not lead one skilled in the art to using the methods and materials cited in the zur Megede post-filing reference. See MPEP 608.01(p). In addition, the zur Megede reference does not disclose which amino acids encoded by SEQ ID NO: 1-4 or nucleotides of SEQ ID NOs: 1-4 are considered essential for eliciting a cellular and/or a humoral immune response.

In addition, Example 14 in the Patent Office's "Synopsis of Application of Written Description Guidelines" is part of training material and is not cited in the MPEP for determining whether a rejection under 112 first paragraph written description applies to a claimed invention. "The Guidelines do not constitute substantive rulemaking and hence do not have the force and effect of law. They are designed to assist Office personnel in analyzing claimed subject matter for compliance with substantive law. Rejections will be based upon the substantive law, and it is these rejections, which are appealable. Consequently, any perceived failure by Office personnel to follow these Guidelines is neither appealable nor petitionable.." See MPEP 2163.

With respect to applicants' argument that the cited cases are not relevant, the argument is not found persuasive because as pointed by applicants both cases are directed to whether possession of a species can describe possession of a genus. This is the case here.

With respect to University of California v. Eli Lilly and Co. (CA FC) 43 USPQ2d 1398, the claimed genus of polynucleotides reads on a polynucleotide encoding an HIV gag polypeptide that elicits a gag-specific immune response and retains any HIV endogenous gag activity. The claimed genus of polynucleotides are not described by general language of patent's written description supported only by specific nucleotide sequence of SEQ ID NO: 1-4. The claimed genus reads on synthetic HIV gag encoding polynucleotides, wherein the HIV gag polypeptide elicits a Gag specific immune response and has any HIV Gag biological activity. In view of the lack of description in the specification for which nucleotides encode a Gag polypeptide that elicits a Gag specific immune response and has any Gag endogenous biological activity, one skilled in the art would not be able to distinguish if a polynucleotide sequence had or did not have nucleotides that encode a Gag polypeptide that elicits a Gag specific immune response and has any endogenous Gag biological activity. The specification does not include examples providing process for obtaining a claimed genus of HIV-gag encoding polynucleotides, and does not describe polypeptides that polynucleotides encode and provides no information, such as sequence information indicating which nucleotides constitute synthetic HIV polynucleotide with the claimed functions and HIV polynucleotides without the claimed functions, pertaining to that polynucleotide's relevant structure or physical characteristics. description which renders claimed invention obvious is not sufficient to satisfy written description requirement of that invention, since claim to specific DNA is not made obvious by mere knowledge of desired protein sequence and methods for generating DNA that encodes that protein, and since description that does not render claimed invention obvious therefore does not sufficiently describe that invention for purposes of 35 USC 112.

With respect to See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993), the specification contains statements that the claimed genus of polynucleotides is part of invention, and reference to potential method for isolating sequence, does not satisfy written description requirement of 35 USC 112, since specification does not describe DNA itself, nor even demonstrate that disclosed method would actually produce DNA in question, and since application therefore does not demonstrate that inventor had possession of claimed DNA.

The Declaration by Jeffrey Ulmer under 37 CFR 1.132 filed 5/20/04 is insufficient to overcome the rejection of claims 1-4, 7-10, 24-43, 49-60 and 63-66 based upon 112 written description as set forth in the last Office action because: in view of the lack of written description for the claimed polynucleotide sequences, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Dr. Ulmer states, "The claims indicate that the polynucleotide must exhibit 90% homology to a reference sequence and it was widely known how to determine sequence identity to any length polynucleotides. Such methods are described in detail in the specification, for example, on pages 19-21 of the specification." The statements by Dr. Ulmer are insufficient to overcome the written description rejection of record because the statement "it was widely known how to determine sequence identity to any length polynucleotides" indicates that applicants were not in possession of the claimed genus of polynucleotide sequences because one skilled in the art would have to make a polynucleotide sequence and determine without guidance from the specification if the sequence meets the limitation of the claimed genus. The statements also

indicate that the applicants were in possession of assays for determining a genus of polynucleotide sequences, but were not in possession of the claimed genus of polynucleotide sequences.

Dr. Ulmer further states, "Methods of testing Gag polypeptides for their ability to elicit Gag-specific immune response were well known at the time of filing and are demonstrated, for example in Exhibit B." The statement by Dr. Ulmer is insufficient to overcome the written description rejection of record because this statement indicates that applicants were in possession of assays for determining the claimed genus of polynucleotide sequences, but were not in possession of the claimed genus of polynucleotide sequences. In addition, with respect to the post-filing article cited by Dr. Ulmer, the specification does not lead one skilled in the art to the evidence set forth in Exhibit B published several years after the filing date of the specification.

Dr. Ulmer further states, "The amino acid sequences of many Gag antigens were known at the time of filing and, in addition, methods of determining other were clearly available as of the date of the application was filed. See, e.g., pages 12, lines 19-27, Exhibit E, Exhibit F. Futhermore, those of us working in the field knew, at the time of filing, that any given antigen can tolerate a number of amino acid substitutions while retaining its immunogenic function." The statement by Dr. Ulmer is insufficient to overcome the written description rejection of record because Exhibits E and F were already addressed in the above response to applicants' arguments. With respect to page 12, lines 19-27, the specification recites that, "antigen can be derived from any of several known viruses, bacteria, parasites and fungi." Page 12, lines 19-27 in the specification further recites that any modification can be made to the antigen. This citation does not specifically disclose modifying the amino acids encoded by SEQ ID NOs: 1-4 and/or

which amino acids encoded by SEQ ID NOs: 1-4 can be modified to retain a humoral and/or cellular immune response. In addition, the citation does not disclose which amino acids can be modified, while Gag activity is maintained.

The statement "Furthermore, those of us working in the field knew, at the time of filing, that any given antigen can tolerate a number of amino acid substitutions while retaining its immunogenic function." The statement is insufficient to overcome the 112 written description rejection because the claims still read on a genus of polynucleotides that encode an HIV Gag polypeptide that elicits a specific Gag immune response and has the biological functions of a natural HIV Gag polypeptide. In addition, Johnson (Exhibit F) teaches that, "Although it appears likely that CTL specific for these conserved gag epitopes will recognize sequences from a variety of HIV-1 isolates, prior studies of the consequences of aa variation in HIV-1 epitopes have shown variable effects on recognition by human HIV-1 specific CTL (page 1519)."

Claims 1-4, 7-10, 24-43, 49-60, and 63-66 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an expression cassette comprising the polynucleotide sequence set forth in SEQ ID NOs: 1, 2, 3, or 4, does not reasonably provide enablement for a polynucleotide sequence encoding an HIV Gag polypeptide, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3 or 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention lies in the field of producing an immunogenic composition using an expression cassette comprising an HIV Gag polypeptide set forth in SEQ ID NOs: 1-4.

In the specification, the applicants contemplate: 1) Expression assays for the synthetic coding region of Gag and Gag-protease expression cassettes; 2) In vivo immunogenicity of Gag expression cassettes using plasmid DNA carrying the synthetic Gag expression cassette; 3) In vitro expression of recombinant alphavirus vectors or plasmid containing the synthetic Gag expression cassette; 4) In vivo immunogenicity of recombinant Sindbis replicon vectors containing Gag expression cassettes in mice by using intramuscular and subcutaneous routes.

The applicants further claim that these experiments will exhibit increased potency for induction of cytotoxic T-lymphocytes (CTL) response and humoral immune response by using the Gag expression cassette.

The as-filed specification provides sufficient guidance for one skilled in the art to make an immunogenic composition comprising an expression cassette comprising of SEQ ID NO: 3 or 4 (and SEQ ID NO: 1 or 2). However, the as-filed specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use a sequence having at least 90% identity to any of the sequences presented as SEQ ID NO: 1-4 other than the sequences themselves.

The claimed invention is directed to a polynucleotide encoding an HIV Gag polypeptide that elicits a Gag-specific immune response, wherein the polynucleotide sequence comprises a nucleotide sequence having at least 90% sequence identity to

the sequences presented in SEQ ID NO: 1, 2, 3, and 4. The specification does not define the term "an HIV Gag polypeptide that elicits a Gag-specific immune response". The specification defines an "immunological response" as humoral and/or cellular immune response (page 14) and the cellular immune response could include a response with CD4+ cells and/or CD8+ cells. The specification does not disclose which nucleotides are considered essential for eliciting a humoral and/or cellular immune response. The claims also read on an the polynucleotide encoding an HIV Gag polypeptide having endogenous Gag polypeptide activity and the specification does not provide sufficient guidance for what nucleotides of any of the claimed sequences or amino acids encoded by the claimed sequences may be changed while endogenous Gag polypeptide activity is retained. The prior art describes the function of HIV-1 Gag proteins in the virus life cycle as exemplified by Freed, where Freed states that, "the role played by HIV-1 Gag proteins during the life cycle are numerous and complex, involving not assembly but also virion maturation after particle release and early post-entry steps in virus replication".

In addition, the nature of the invention is directed to a polynucleotide sequence encoding an HIV Gag polypeptide that elicits a specific Gag immune response, wherein the polynucleotide comprises a nucleic acid sequence that has 90% identity to SEQ ID NO: 1-4. SEQ ID NO: 1 is a fragment of SEQ ID NO: 3 and SEQ ID NO: 2 is a fragment of SEQ ID NO: 4. The scope of the invention is very broad, encompassing a large number of polynucleotide sequences that may or may not encode an HIV Gag polypeptide that may or may not have the desired activity. A

search of SEQ ID NO: 4 (1509 nucleotides) indicates that SEQ ID NO: 3 (1479 nucleotides) is 84.6% identical to SEQ ID NO: 4. The same nucleotide search of SEQ ID NO: 4 indicates that it has 98.7% sequence identity to SEQ ID NO: 21 and 83.6% sequence identity to SEQ ID NO: 20. Other than the nucleic acid sequences of SEQ ID NO: 3 and 4 and fragments of SEQ ID NO: 3 (SEQ ID NO: 1) or SEQ ID NO: 4 (SEQ ID NO: 2); and SEQ ID NO: 20 and 21, the specification fails to disclose any other nucleic acid sequences encoding a polypeptide with Gag activity. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Baker et al., Science, 294:pages 93-96, 2001); Attwood, T (*Science*, vol. 290, no. 5491, pp. 471-473, 2000); Gerhold et al., (*BioEssays*, vol. 18, no. 12, pp. 973-981, 1996); Russell et al., *Journal of Molecular Biology*, vol. 244, pp 332-350, 1994); and Wells et al., *Journal of Leukocyte Biology*, vol. 61, no. 5, pp. 545-550, 1997). Also, since the relationship of the sequence of a peptide and its tertiary structure (*e.g.* its activity) are not well understood and are not predictable (Ngo et al. The Protein Folding Problem and

Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one skilled in the art in view of the prior art to arrive at other sequences that have at least 90% sequence identity to the Gag polypeptide encoded by SEQ ID NOs: 1-4 and still possess HIV Gag polypeptide activity.

In addition, the claims are broader than the guidance or factual evidence provided by the as-filed specification because the claims embrace a polypeptide with 70% identity to the HIV gag polypeptide encoded by SEQ ID NOs: 1-4. There is no guidance in the specification as to which amino acids encoded by the polynucleotide sequence set forth SEQ ID NO: 3 or SEQ ID NO: 4 may be changed while endogenous HIV Gag activity is retained and the HIV Gag polypeptide is still immunogenic. As stated above, the teaching in the as-filed specification does not commensurate in scope with the claims because the breadth of the claims embrace a large number of possible sequences that differ from the polynucleotide sequence set forth in SEQ ID NO: 1-4. The claims are broader than the 90% limitation set forth in the claims because the polypeptide sequences embraced by the polynucleotide sequences having 90% identity to SEQ ID NO: 1-4 can have a substitution of at least 30% of the amino acids of the polypeptides encoded by the claimed sequences, which would be a substitution of up to 150 amino acids of the polypeptide encoded by either SEQ ID NO: 3 or 4 and a substitution of up to 6 amino acids of the polypeptide encoded by either SEQ ID NO: 1 or 2. The number of single amino acid substitutions for an amino acid sequence encoded by the polynucleotide sequence set forth in SEQ

ID NO: 3 or 4 is 9,500. The number of two amino acids substitutions for an amino acid sequence encoded by SEQ ID NO: 3 or 4 is over 9.0×10^7. The number of single amino acid substitutions for an amino acid sequence encoded by the polynucleotide sequence set forth in SEQ ID NO: 1 or 2 is 380. The number of two amino acids substitutions for an amino acid sequence encoded by SEQ ID NO: 1 or 2 is over 1.4×10^5. To determine the number of possible amino acid sequences encoded by the polypeptide encoded by the polynucleotide sequence set forth in SEQ ID NO: 3 or 4, N, with substitutions, one skilled in the art would use the formula $[(N=x^nL!/n!(L-n)!)$, where x=19 (number of possible amino acids that could replace an amino acid at any one position in the polypeptide encoded by SEQ ID NO: 3 or 4), L=500 (estimated amino acid length of the polypeptide encoded by SEQ ID NO: 3 or 4), n=150,] or $1.1x10^{323}$ possible sequences. This is a lower limit of the number of possible sequences because the claims also embrace insertions or deletions of amino acids in the polypeptide sequence encoded by SEQ ID NO: 3 or 4 that the equation does not take into account. In addition, with respect to the polypeptide sequences encoded by the polynucleotide sequences set forth in SEQ ID NO: 1 and 2 and using the above formula, the number of possible sequences for the polypeptide encoded by SEQ ID NO: 1 or 2 is $1.8x10^{12}$. This is a lower limit of the number of possible sequences because the claims also embrace insertions or deletions of amino acids in the polypeptide sequence encoded by SEQ ID NO: 1 or 2 that the equation does not take into account.

In conclusion, the as-filed specification and the claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable making and using an expression cassette comprising the polynucleotide sequence set forth in SEQ ID NOs: 1-4, does not reasonably provide enablement for a polynucleotide sequence encoding an HIV Gag polypeptide that elicits a specific Gag immune response, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3 or 4. One would have to engage in a large quantity of excessive and undue experimentation in order to practice the claimed invention based on the In Re Wands Factors including the lack of guidance in the application's disclosure, the unpredictability of producing nucleotide sequences encoding a HIV Gag polypeptide with 90% sequence identity to the claimed SEQ ID NOs. In addition, the prophetic examples as provided in the specification do not reasonably extrapolate to the full scope of the claimed invention because one skilled in the art would have to make a nucleotide sequence and determine if the sequence meets the limitations set forth in the claims.

Applicant's arguments filed 5/20/04 have been fully considered but they are not found persuasive because in view of the In Re Wands Factors, the as-filed specification does not provide sufficient guidance for one skilled in the art to practice the full scope of the claimed invention.

With respect to applicant's argument that the relationship between tertiary structure and non-immunogenic activities (such as VLP formation) is irrelevant, the argument is not found

persuasive because the claims still embrace an HIV gag polypeptide with non-immunogenic activities (such as VLP formation). The amendment does not exclude the claims from embracing a polynucleotide sequence encoding an HIV Gag polypeptide with non-immunogenic biological activities. There is not guidance in the specification as to what 10% of the polynucleotide can be changed while maintaining a polypeptide having the ability to elicit an HIV Gag specific immune response and having endogenous HIV Gag activity. The prior art teaches that one skilled in the art cannot consult the prior art in order to make a nucleotide sequence having 90% identity to SEQ ID NO: 1-4 encoding an HIV Gag polypeptide with the ability to elicit a specific HIV gag immune response and have endogenous HIV Gag activity. Furthermore, the skilled artisan would be required to empirically determine the function of each polypeptide having 70% identity the HIV Gag polypeptide encoded by the polynucleotide sequences set forth in SEQ ID NO: 1-4. This would require a large amount of undue and unpredictable trial and error experimentation.

Applicants' argue that: the examiner errs in setting forth percent identity to polypeptides encoded by SEQ ID NOs: 3 and 4. The fact that there are a vast number of 500 amino acid peptides is of no consequence to the pending claims. Taken in isolation, the 90% identity limitation requires a maximum substitution of 6 substitutions in the reference sequences of claims 1 and 3 and approximately 150 substitutions in the reference sequences of claims 2 and 4. The claims now clearly recite a single reference sequence and require that any and all sequence falling within the scope of the claims exhibit percent identity to the that sequence and also exhibit the claimed functionality. In view of the clear disclosure regarding structure and

methods of making and testing polypeptides from these structures, the experimentation is clearly not undue, but merely routine.

With respect to applicants' argument that the examiner errs in setting forth the percent identity, while it is acknowledged that the examiner did make an error in setting forth percent identity because the examiner used 10% of 500 in the equations instead of 30% of 500. The issue has been corrected in the enablement rejection set forth above. The arguments are still not found persuasive because the claims remain broader than the enabling disclosure and there is no guidance in the specification as to which (if any) of the amino acids encoded by the polynucleotide sequences set forth in SEQ ID NO: 1-4 may be changed while endogenous HIV Gag activity is retained and the polypeptide retains a humoral and/or cellular immune response activity.

With respect to applicants' argument that "The fact that there are a vast number of 500 amino acid peptides is of no consequence to the pending claims" and "The claims now clearly recite a single reference sequence and require that any and all sequence falling within the scope of the claims exhibit percent identity to the that sequence and also exhibit the claimed functionality. In view of the clear disclosure regarding structure and methods of making and testing polypeptides from these structures, the experimentation is clearly not undue, but merely routine", the arguments are not found persuasive because in view of the lack of specification for providing sufficient guidance or factual evidence for what domains/portions of the HIV gag polypeptide are required in order to maintain endogenous HIV gag activity and elicit a specific HIV Gag immune response nor is there any indication of what functions/activities a protein having 70% sequence identity might have as a result of the 30% changes in amino acid

sequences and the state of the art is silent with regard to polypeptides having 70% identity to the polypeptides encoded by the polynucleotide sequences set forth in SEQ ID NO: 1-4, it would take one skilled in the art a large amount of undue and unpredictable trial and error experimentation to determine which polypeptides are embraced by the claims.

With respect to applicants' argument that "Taken in isolation, the 90% identity limitation requires a maximum substitution of 6 substitutions in the reference sequences of claims 1 and 3 and approximately 150 substitutions in the reference sequences of claims 2 and 4", the argument is not found persuasive because the activity of HIV Gag is directed to its amino acid sequence and the examiner discusses the rejection based on the polypeptide sequence encoded by SEQ ID NO: 1 to display the breadth of the claims. In addition, the claims also read on sequences with insertions and deletions and the number of possible substitutions would be more than a maximum of 6 substitutions with respect to claims 1 and 3 or 150 substitutions with respect to claims 2 and 4. Furthermore, there is no indication in the specification for what domains/portions of the HIV gag polypeptide are required in order to maintain endogenous HIV gag activity and elicit a specific HIV Gag immune response nor is there any indication of what functions/activities a protein having 70% sequence identity might have as a result of the 30% changes in amino acid sequences.

In addition, In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states:

> Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements, while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or

> electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

This is the case here. Neither the specification nor the prior art provide a known scientific law for modifying several nucleotides of a sequence and predicting the biological function of the modified sequence.

Furthermore, applicants argue that the specification as filed provides clear examples of substitutions/deletions as compared to the reference sequence, namely SEQ ID NOs: 3 and 4 and fragments of SEQ ID NO: 3 (SEQ ID NO: 1) and 4 (SEQ ID NO: 2); the additional evidence (Declaration of record, Ulmer's Declaration and Exhibits E and F) fully supports the specification's teaching that the Gag polypeptides were well characterized in terms of immunogenicity. In addition, applicants remind the examiner that the specification does not need to teach in detail that which is conventional or well known. The argument is not found persuasive because the claimed polynucleotide sequence still read on a sequence that encodes an HIV Gag polypeptide that elicits a specific immune response and has the activity of a wild type HIV Gag protein. In addition, the Declaration of Dr Donnelly, Ulmer's Declaration and Exhibits E and F do not provide that the specification provided sufficient guidance or factual evidence to support the claimed genus of polynucleotides. The declaration by Dr. Donnelly does not address making and using a genus of polynucleotide sequences encoding an HIV gag polypeptide that elicits a cellular and/or a humoral immune response. Parker (Exhibit E) teaches a scheme for ranking potential HLA-A2 binding peptide based on independent binding of individual side-chains using synthetic nonamer peptides. Parker does not teach that immunogenic regions for

eliciting a cellular and/or humoral immune response of an HIV gag polypeptide based on SEQ ID NOs: 1-4 were known at the time the invention was made. The specification does not teach using the scheme taught by Parker for determining which amino acids of an HIV gag polypeptide comprising of at least amino acids of SEQ ID Nos: 1-4 are required for eliciting a gag-specific immune response. See MPEP 608.01(p). Johnson identifies epitopes in the HIV-1 gag protein and the heterogeneity of CTL responses to this protein. Johnson further teaches that, "Although it appears likely that CTL specific for these conserved gag epitopes will recognize sequences from a variety of HIV-1 isolates, prior studies of the consequences of aa variation in HIV-1 epitopes have shown variable effects on recognition by human HIV-1 specific CTL (page 1519)." The specification does not teach how to correlate the epitopes from the HIV-gag proteins taught by Johnson with the claimed genus of polynucleotide sequences. See MPEP 608.01(p). The specification does not teach using peptides and the assay taught by Johnson or Parker for determining which amino acids of an HIV gag polypeptide comprising are required for eliciting a gag-specific immune response. See MPEP 608.01(p). Thus, nothing in specification provides support that the Gag polypeptides that elicit a Gag-specific immune response were well characterized in terms of immunogenicity and that immunogenicity may be retained when amino acid substitutions are made.

In addition, with respect to applicants' arguments that the newly cited references in the last office action all relate to difficulties in predicting the function of an unknown and uncharacterized polypeptide encoded by a similarly uncharacterized polynucleotide and do not establish unpredictability, the argument is not found persuasive because the specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to

screen at least $1.1x10^{323}$ sequences for amino acid peptides encoded by SEQ ID NO: 3 or 4 or $1.8x10^{12}$ sequences for amino acid peptides encoded by SEQ ID NO: 1 or 2 that meet or do not meet the limitations set forth in the claims. In addition, the claimed invention embraces unknown and uncharacterized polypeptides encoded by uncharacterized polynucleotides and the cited references teach the unpredictability of the relationship between sequence and function of uncharacterized polypeptides.

Applicants argue that the Enzo case cited in the office action is not relevant because the applicants reiterate that unpredictability of the claimed invention has not been established by the newly cited references and the Enzo's facts are completely different than those in the case at hand and Enzo does not relate to the question of enablement of sequences; Enzo actually supports Applicants' arguments that their specification fully enables claims that encompass only sequences exhibiting the requisite high level of homology to a reference sequence and recited function. The examiner acknowledged that Enzo is directed to the use of a genus of DNA constructs in cells. However, the principle of the case is directed to the breadth of enablement was not commensurate in scope with the claims and using the In Re Wands Factors to show that the full scope of the claimed invention was not enabled. This is the case here. The amount of direction presented and the number of working examples provided in the specification were very narrow compared to the wide breadth of the claims at issue (at least $1.1x10^{323}$ amino acid peptides are embraced by only polypeptide encoded by claimed SEQ ID NO: 3), predicting function of an amino acid based on its nucleotides sequence was unpredictable, and the amount of experimentation required to adapt the practice of is excessive and undue (screen at least

$1.1x10^{323}$ amino acid peptide for peptides that meet or do not meet the limitations set forth in the claims).

The Declaration by Jeffrey Ulmer under 37 CFR 1.132 filed 5/20/04 is insufficient to overcome the rejection of claims 1-4, 7-10, 24-43, 49-60 and 63-66 based upon 112 enablement as set forth in the last Office action because: in view of the In Re Wands Factors, the as-filed specification does not provide sufficient guidance or factual evidence for one skilled in the art to practice the full scope of the claimed invention.

> MPEP 716.01(c) recites: In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986).

Dr. Ulmer states, "In December 1999, the quantity of experimentation required to identify sequences exhibiting 90% identity to any given sequence for example SEQ ID NOs: 1-4, was quite low." The statement is insufficient to overcome the 112 enablement rejection of record because the rejection is not arguing that one skilled in art can identify sequences exhibiting 90% identity to any given claimed sequence, the rejection is based on the In Re Wands Factors and given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it was concluded that the skilled artisan would have needed to have conducted undue and excessive experimentation in order to

practice the claimed invention. Thus, the as-filed specification fails to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen at least $1.1x10^{323}$ sequences for amino acid peptides encoded by SEQ ID NO: 3 or 4 or $1.8x10^{12}$ sequences for amino acid peptides encoded by SEQ ID NO: 1 or 2 that meet or do not meet the limitations set forth in the claims.

Dr. Ulmer states, "In addition, the specification provides significant direction for evaluating whether sequences having 90% identity to SEQ ID NO: 1-4 encode an immunogenic Gag polypeptide." The statement is insufficient to overcome the 112 enablement rejection of record because as stated in rejection set forth in the instant office action, the specification does not define an HIV Gag polypeptide that elicits a Gag-specific immune response. The specification defines an "immunological response" as humoral and/or cellular immune response (page 14) and the cellular immune response could include a response with CD4+ cells and/or CD8+ cells. The specification does not provide sufficient guidance and/or factual evidence for which nucleotides are considered essential for eliciting a humoral and/or cellular immune response.

Dr. Ulmer further states:

> Even if a rare construct were inoperable for some reason, the skilled worker would have readily modified the construct according to the alternative available at the time and described in the specification. In other words, to the skilled worker, an inoperably construct would itself be useful starting material for another operably constructs. Essentially all molecules that fall within the claims would be useful for making and using defining technical features of the claims.

The statement is insufficient to overcome the 112 enablement rejection of record because it appears that the statement is addressing a 101 utility rejection for how to use inoperable embodiments embraced by the claims. The rejection is under 112 first paragraph enablement and is directed to whether it would take one skilled in the art an undue amount of experimentation to make and use the claimed genus of polynucleotide sequences. The specification and the prior art fail to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen at least $1.1x10^{323}$ sequences for amino acid peptides encoded by SEQ ID NO: 3 or 4 or $1.8x10^{12}$ sequences for amino acid peptides encoded by SEQ ID NO: 1 or 2 that meet or do not meet the limitations set forth in the claims.

Dr. Ulmer states, "In view of the guidance in the specification, the predictability and state of the art, and high level of the skilled worker, it is plain that it would have been routine to administer a polynucleotide and evaluate whether or not an immune response to the encoded polypeptide was generated in the subject." The statement is insufficient to overcome the 112 enablement rejection of record because the specification must be enabling as of the filing date. See MPEP 2164.05(a). The statement by Dr. Ulmer indicates that one skilled in the art would have to evaluate whether or not an immune response (humoral and/or cellular) was generated against a polypeptide encoded by an administered claimed polynucleotide. The specification and prior art fail to provide sufficient guidance and/or factual evidence that it was routine for one skilled in the art to screen at least $1.1x10^{323}$ sequences for amino acid peptides encoded by SEQ ID NO: 3 or 4 or $1.8x10^{12}$ sequences for amino acid peptides encoded by SEQ ID NO: 1 or 2 that meet or do not meet the limitations set forth in the claims.

Dr. Ulmer states, "Experiments conducted after the filing date of the application also demonstrate that the expression cassettes that include modified HIV Gag-encoding sequences induce potent Gag specific immune responses (Zur Megede et al., 2003 J. Virol. 77:6197-6207, Exhibit B). Dr. Ulmer further states, "Furthermore, because Gag-encoding sequences can be obtained from any HIV isolated and modified as described in the specification, the results we presented in the Exhibit B with regard to subtype B sequences are equally applicable to modified polynucleotides from subtype C isolates as claimed." The statements with respect to the post-filing article are insufficient to overcome the rejection of record because the specification must be enabling as of the filing date. See MPEP 2164.05(a). In addition, in view of the specification not teaching how to correlate the results with subtype B sequences in the post-filing art to making and using subtype C isolates, the statements by Dr. Ulmer are not sufficient to overcome the 112 enablement rejection of record. See MPEP 608.01(p).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites the limitation "said transcription promoter" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Claim 24 from which claim 26 depends from does not recite a transcription promoter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(f) he did not himself invent the subject matter sought to be patented.

Claims 3, 8, 9, 10, 24-40, 67, and 74 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The claims from the instant application are directed to an expression cassette comprising a polynucleotide sequence operably linked to a promoter, wherein the polynucleotide sequence encodes an HIV Gag polypeptide with 90% sequence identity to the sequence encoding an HIV Gag polypeptide set forth in a particular SEQ ID NO: 2.

The claims from US Patent 6,602,705 are directed to an expression cassette comprising a nucleotide sequence encoding a Gag polypeptide with 90% sequence identity to a Gag polypeptide set forth in a particular SEQ ID NOs: 4, 9, 20, 78, 79, which have 90% sequence identity to SEQ ID NO: 2 in the instant application. Furthermore, the claims recite using a promoter operably linked to the polynucleotide sequence.

Claims 1-4, 67, 68, 69, and 74-75 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The claims from the instant application are directed to an expression cassette comprising a polynucleotide sequence operably linked to a promoter, wherein the polynucleotide sequence

encodes an HIV Gag polypeptide with 90% sequence identity to the sequence encoding an HIV Gag polypeptide set forth in a particular SEQ ID NO: 1 and 2.

The claims of co-pending application 09/899,575 are drawn to an expression cassette comprising a polynucleotide comprising x contiguous nucleotides, wherein (i) the X contiguous nucleotides have at least 90% identity to Y contiguous nucleotides of SEQ ID NO: 51, 99, or 68 (claims 7, 8, and 16, respectively). SEQ ID NO: 51 in claim 7 and SEQ ID NO: 99 in claim 8 are 100% identical to SEQ ID NO: 1 in the instant application. In addition, SEQ ID NO: 68 is 100% identical to SEQ ID NO: 2 of the instant application.

Claims 1-6, 24, 27, 41, 42, 43, 67-74 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The claims from the instant application are directed to an expression cassette comprising a polynucleotide sequence operably linked to a promoter, wherein the polynucleotide sequence encodes an HIV Gag polypeptide with 90% sequence identity to the sequence encoding an HIV Gag polypeptide set forth in a particular SEQ ID NO: 1-4.

The claims from copending application 09/967,464 claim a microparticle comprises a vector comprising a heterologous nucleic acid sequence that encodes an HIV Gag polypeptide having a sequence having at least 90% identity to nucleotides 844-903 of SEQ ID NO: 63 (100% identity with SEQ ID NO: 1 and 3), nucleotides 841-900 of SEQ ID NO: 64 (100% identity to SEQ ID NO: 1 and 2), nucleotides 82-1512 of SEQ ID NO: 68 (100% identity to SEQ ID NO: 2 and 99% identity to SEQ ID NO: 4). Although the claims do not specifically recite a promoter operably linked to the heterologous nucleic acid it would be inherent that the vector comprising

the heterologous nucleic acid also have a promoter to express the heterologous nucleic acid because a promoter is required for the heterologous to be expressed in a cell.

Double Patenting

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 67, 68, 69, and 74-75 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 8, and 16 of co-pending Application No. 09/899,575. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of co-pending application '575 are drawn to an expression cassette comprising a polynucleotide comprising x contiguous nucleotides, wherein (i) the X contiguous nucleotides have at least 90% identity to Y contiguous nucleotides of SEQ ID NO: 51, 99, or 68 (claims 7, 8, and 16, respectively). SEQ ID NO: 51 in claim 7 and SEQ ID NO: 99 in claim 8 are 100% identical to SEQ ID NO: 1 in the instant application. In addition, SEQ ID NO: 68 is 100% identical to SEQ ID NO: 2 of the instant application. Furthermore, claims 74 and 75 of the instant application '704 are obvious variants of claims 7, 8, and 16 of co-pending application '575 because the only difference

between clams 74-75 of the instant application and claims of co-pending application '575 is using the expression cassette in a composition for producing an immune response in a mammal and a method of using the composition. One of ordinary skill in the art would have concluded that the invention defined in the claims in the instant application '704 is an obvious variant of the invention defined in the claims of the co-pending application '575.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed 5/20/04 have been fully considered but they are not persuasive. The rejection remains because the claims are not in condition for allowance and Applicants have not provided a terminal disclaimer to overcome the double patenting rejection.

Claims 3, 8, 9, 10, 24-40, 67, and 74 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 and 10-30 of U.S. Patent No. 6,602,705. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims from the instant application are directed to an expression cassette comprising a nucleotide sequence encoding a Gag polypeptide with 90% sequence identity to a Gag polypeptide set forth in a particular SEQ ID NO: 2. The claims from the '705 are directed to an expression cassette comprising a nucleotide sequence encoding a Gag polypeptide with 90% sequence identity to a Gag polypeptide set forth in a particular SEQ ID NOs: 4, 9, 20, 78, 79, which have 90% sequence identity to SEQ ID NO: 2 in the instant application.

Claims 1-6, 24, 27, 41, 42, 43, 67-74 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26, 28, 31-50, and 72 of copending Application No. 09/967,464 (US pre-grant publication 2003/0138453).

The claims from the instant application are directed to an expression cassette comprising a nucleotide sequence encoding a Gag polypeptide, wherein the nucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to SEQ ID NOs: 1-4. The claims from copending application '464 claim a microparticle comprises a vector comprising a heterologous nucleic acid sequence that encodes an HIV Gag polypeptide having a sequence having at least 90% identity to nucleotides 844-903 of SEQ ID NO: 63 (100% identity with SEQ ID NO: 1 and 3), nucleotides 841-900 of SEQ ID NO: 64 (100% identity to SEQ ID NO: 1 and 2), nucleotides 82-1512 of SEQ ID NO: 68 (100% identity to SEQ ID NO: 2 and 99% identity to SEQ ID NO: 4).

This is a provisional obviousness-type double patenting rejection.

Claims 1, 3, 67, and 74-75 directed to an invention not patentably distinct claims 1-5 and 10-30 of commonly assigned US Patent 6,602,705. Specifically, the claims from the instant application are directed to an expression cassette comprising a nucleotide sequence encoding a Gag polypeptide with 90% sequence identity to a Gag polypeptide set forth in a particular SEQ ID NO: 2. The claims from the '705 are directed to an expression cassette comprising a nucleotide sequence encoding a Gag polypeptide with 90% sequence identity to a Gag

polypeptide set forth in a particular SEQ ID NOs: 4, 9, 20, 78, 79, which have 90% sequence identity to SEQ ID NO: 2 in the instant application.

Claims 1-4, 67, 68, 69, and 74-75 are directed to an invention not patentably distinct from claims 7, 8, and 16 of commonly assigned US application 09/899,575. Specifically, the claims of co-pending application '575 are drawn to an expression cassette comprising a polynucleotide comprising x contiguous nucleotides, wherein (i) the X contiguous nucleotides have at least 90% identity to Y contiguous nucleotides of SEQ ID NO: 51, 99, or 68 (claims 7, 8, and 16, respectively). SEQ ID NO: 51 in claim 7 and SEQ ID NO: 99 in claim 8 are 100% identical to SEQ ID NO: 1 in the instant application. In addition, SEQ ID NO: 68 is 100% identical to SEQ ID NO: 2 of the instant application. Furthermore, claims 74 and 75 of the instant application '704 are obvious variants of claims 7, 8, and 16 of co-pending application '575 because the only difference between clams 74-75 of the instant application and claims of co-pending application '575 is using the expression cassette in a composition for producing an immune response in a mammal and a method of using the composition.

Claims 1-6, 24, 27, 41, 42, 43, 67-74 are directed to an invention not patentably distinct from claims of commonly assigned copending application 09/967,464. Specifically, the claims from the instant application are directed to an expression cassette comprising a nucleotide sequence encoding a Gag polypeptide, wherein the nucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to SEQ ID NOs: 1-4. The claims from copending application '464 claim a microparticle comprises a vector

comprising a heterologous nucleic acid sequence that encodes an HIV Gag polypeptide having a sequence having at least 90% identity to nucleotides 844-903 of SEQ ID NO: 63 (100% identity with SEQ ID NO: 1 and 3), nucleotides 841-900 of SEQ ID NO: 64 (100% identity to SEQ ID NO: 1 and 2), nucleotides 82-1512 of SEQ ID NO: 68 (100% identity to SEQ ID NO: 2 and 99% identity to SEQ ID NO: 4).

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned us application, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Scott D Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635